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ENERGETIC PROTON DOSE-RESPONSE

The Relative Biological Effectiveness of Energetic Protons in the Induction of Head and Neck Tumors in Rats

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TABLE OF CONTENTS

List of Illustrations	3
Abstract.	4
Introduction.	5
Background	5
Objective.....	6
Methods and Materials.....	7
Results	8
Discussion and Conclusions.....	15
Appendix A: Individual Subject Tumor Data (Proton Exposures)	18
Appendix B: Individual Subject Tumor Data (Cobalt Exposures).....	34

LIST OF ILLUSTRATIONS

Figure 1. Dosimetry model of a rhesus monkey head rotated in a beam of 55-MeV protons.....	6
Figure 2. Restraint device for head-only exposure of rats to the proton beam at the Harvard University Cyclotron Laboratory.	7
Figure 3. Kaplan-Meier survival probability of male F-344 rats after head-only exposure to Bragg Peak protons.	10
Figure 4. Kaplan-Meier survival probability of male F-344 rats after head-only exposure to ^{60}Co γ -radiation.....	11
Figure 5 Incidence density plot of all head and neck tumors by dose group.	12
Figure 6. Incidence density plot of brain tumors by dose group.....	12
Figure 7. Life span incidence of head and neck tumors by primary cell type.....	13
Figure 8. Life span incidence of mononuclear cell leukemia in rats exposed to head-only proton or ^{60}Co γ -radiation.....	14
Table 1. Survival (Weeks) of Male F-344 Rats after Head-Only Irradiation.	10

Abstract

In previous lifespan studies sponsored jointly by The National Aeronautics and Space Administration and the United States Air Force, rhesus monkeys that were given total body surface exposures of high energy protons experienced an unusual incidence of malignant brain tumors /1/. To investigate the risk of similar tumor occurrence subsequent to solar radiation exposures in humans, 1100 Fischer-344 rats, aged 70 days, were exposed to uniformly distributed head-only doses of spread Bragg Peak protons. They were divided into five dose groups of 200 animals each, with an additional 100 animals for disease control sentinels. The dose groups were zero (sham-irradiated), 2, 4, 8.5 and 18 Gy. Every subject that completed the study received a post-mortem examination including serial sections of the brain for histological verification of tumor occurrence and type. After the proton study was completed, five additional group of rats of the same age, sex and strain was exposed to head-only ^{60}Co γ -radiation on the same dose and dose rate schedule as the proton-exposed rats and they were maintained and observed under the same conditions. The five dose groups each consisted of 40 animals, with an additional 20 disease control sentinels, for a total of 220 rats. Total head and neck tumor incidence for both types of radiation in the dose range of 0-8.5 Gy displayed a linear dose-response. The exposed rats had a greater incidence of tumors, especially pituitary chromophobe adenomas, epithelial tumors and mesenchymal cell tumors, than the unexposed controls, but the excessive occurrence of malignant gliomas that had previously been observed in proton-irradiated monkeys was absent in the rats. The hypothesis that the relative biological effectiveness (RBE) of protons in the induction of head and neck tumors was unity could not be rejected; however, a significant increase in precancerous squamous metaplasia was observed in the proton-exposed rats, but not in the ^{60}Co -exposed animals. We conclude that the occurrence of radiation-induced brain tumors in the rhesus monkeys can be explained by the Bragg Peak dose distribution in susceptible tissues rather than by a high RBE of protons for brain tumor induction.

Introduction

Background. During the period 1964-1969, the U. S. Air Force School of Aerospace Medicine (USAFSAM), with the support of the National Aeronautics and Space Administration (NASA) began an investigation of the immediate and long-term effects of space radiation using immature rhesus monkeys as human surrogates. Monkeys of both sexes were exposed to high-energy protons in various dose and energy combinations to bracket the known spectrum of naturally occurring proton radiation in space. The energies chosen were 32, 55, 138, 400 and 2300 MeV. The life span study included 301 irradiated monkeys and 57 age-matched controls. They were observed continuously to determine the long term effects, especially cancer, cataracts, and lowered life expectancy /1, 2/.

Among the fatal cancers occurring in the monkeys, the most prevalent single type was glioblastoma multiforme, a malignant brain tumor that affected one female and eight males in a group of 72 animals exposed to 55-MeV protons /3/. Protons of this energy will distribute all of their kinetic energy within the first 2.5 cm of tissue, resulting in a non-uniform dose distribution and “hot spots” in the head of a monkey /4/. The surface dose range for the affected monkeys was 4 to 8 Gy, but calculations by the original investigators indicated that some areas of the brain could have received up to three times the measured surface dose because of the Bragg Peak effect /5/. The first brain tumor appeared 18 months after irradiation, while the last occurred 20 years post-exposure. Because most of the internal cranial tumors were not diagnosed until they became symptomatic, they were too large at the time of necropsy for their exact point of origin relative to the body surface to be determined; however, all of the glioblastomas affected areas of the cerebral cortex that could have received more than the measured surface dose of radiation according to the dosimetry models of Leavitt (Figure 1). The short latent period of some of these tumors compared to the latencies reported in known cases of radiation-induced brain tumors in humans (10 years or more) prompted the suspicion that protons might be more effective in tumor induction than the therapeutic radiation treatments that caused secondary tumors later in the life of some human patients. This suspicion was enhanced by the results of concurrent studies of similar aged monkeys that had received whole body doses of 2-MeV x-ray radiation. One of these subjects developed a fatal glioblastoma 284 months after radiation with 5.8 Gy total body

surface dose. This is consistent with the latency that would be expected for tumors that are caused by therapeutic x-rays.

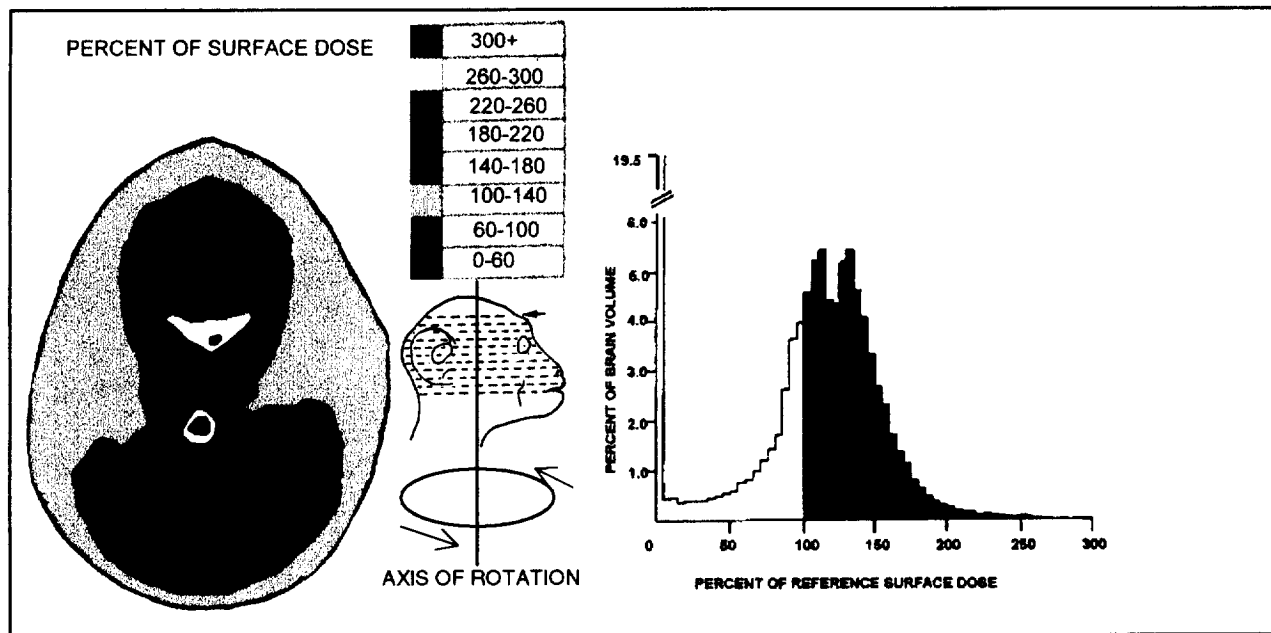


Figure 1. Dosimetry model of a monkey head rotated in a beam of 55-MeV protons (Modified after Leavitt /5/)

Objective. The present study was undertaken to supplement the primate data by utilizing a large population of Fischer-344 rats to establish the dose-response relationship between Bragg Peak energetic protons and tumors of the head and neck, especially brain tumors. Fischer rats are a frequently used model in carcinogenesis studies because of their relatively low spontaneous solid tumor rate and their well-documented positive response to several known carcinogens. In reviewing brain tumor incidence in control groups of Fischer rats used in 2-year carcinogenesis studies, Solleveld et al., reported that the overall incidence was 1.04% among 1928 subjects and that it never exceeded 4% in any single control group of 50 animals /6/. Because normal brain tumor incidence in humans is well documented, establishment of a dose-response curve for brain tumor induction by proton irradiation will aid in the estimation of cancer risk subsequent to space missions and help establish the probability of causation for those tumors that actually do occur in crew members later in life.

The primate studies were all total body surface exposures. In the rats, only the head was exposed in order to obtain a wider range of brain tumor dose-response than would be available if the high-dose animals were subjected to the life-shortening effects of whole body radiation.

Methods and Materials

Proton Exposures. A total of 1100 male Fischer-344 rats*, aged 70 days, were delivered on July 26, 1989 from the supplier to the Harvard Cyclotron Laboratory, Cambridge, MA, 24 hours prior to the scheduled exposures. The test animals were divided into five dose groups of 200 animals each, and an additional 100 animals were retained for disease control monitoring. The dose groups were zero (sham-irradiated), 2, 4, 8.5 and 18 Gy. Unanesthetized animals were irradiated in groups of eight in a circular restraining device, positioned and shielded so that only the heads were exposed to the proton beam (Figure 2). The 138-MeV beam was attenuated by Lucite filters to produce an expanded Bragg Peak that provided a uniform dose distribution across the area of the entire brain at a rate of approximately 1.25 Gy/min. The dosimetry was verified by exposing rat cadavers containing implanted thermoluminescent dosimeters. Sixteen hours after completion on the exposures, a commercial air carrier shipped the rats to the Veterinary Sciences Facility at the Armstrong Laboratory, Brooks AFB, Texas.



Figure 2. Restraint device for head-only exposure of rats to the proton beam at the Harvard University Cyclotron Laboratory.

*CDF® (F-344)/CrIBR, Charles River Laboratories.

During their life span, the subjects were examined twice daily for morbidity and mortality. Subjects that were severely debilitated, in obvious distress, or moribund were euthanatized by carbon dioxide inhalation. At 923 days after irradiation, with less than 2% of the subjects alive, all remaining subjects were killed and examined. Every subject received a post-mortem examination including serial sections of the brain for histological verification of tumor occurrence and type. The Veterinary Pathology Branch at the USAF School of Aerospace Medicine did the tissue processing for the proton study, while Pathology Associates, Inc., Frederick, MD, processed the tissues from the cobalt study.

Cobalt Exposures. The potential value of determining the tumor response to ^{60}Co γ -radiation became apparent after the data began to accumulate in the proton study. The prevalence of some lesions, notably pre-cancerous squamous metaplasia, suggested that the relative biological effectiveness of protons in the induction of some tumors might differ from unity. To test this hypothesis, an additional group of rats of the same age, sex and strain was exposed to head-only ^{60}Co γ -radiation on the same dose and dose rate schedule as the proton-exposed rats and they were maintained and observed under the same conditions. The five dose groups each consisted of 40 subjects, with an additional 20 disease control sentinels, for a total of 220 rats. The cobalt exposures were done at the Southwest Research Institute Cobalt Facility on August 18, 1992 and the last rat died on January 6, 1995, 870 days after irradiation.

Data Analysis. For purposes of data analysis, the tumors of the head and neck were grouped in six categories based on the morphological diagnosis of the lesion:

- Brain and meninges
- Pituitary gland, all parts
- Bone and cartilage
- Epithelium and endothelium
- Thyroid gland (follicular cells and C-cells)
- Miscellaneous tumors of mesenchymal origin

A veterinary pathologist (RWT) who is a Diplomate of the American College of Veterinary Pathology did the tumor identification. He submitted any questionable lesions to the

Armed Forces Institute of Pathology for verification of his findings.

Tumor occurrence in each experimental group was expressed as incidence density, or number of tumors versus time at risk. The incidence densities in the irradiated groups were compared with those of the sham-irradiated groups by the method described by Miettinen for obtaining the null chi-squared value with 1 d.f. for incidence in unequal populations /7/. Additionally, the dose response relationship for brain tumors alone, and for all head and neck tumors combined, was calculated by simple linear regression of the incidence densities of these tumors.

The populations of the dose groups in the final analysis were not uniform, owing to inevitable losses associated in an animal life span study with over 1000 subjects. The large discrepancy in the 18-Gy-proton population occurred when 40 of these subjects were lost due to mishandling by the commercial shipper en route from the Harvard Cyclotron Laboratory to the Armstrong Laboratory. The statistical methodology that we used was selected because equal populations are not a requirement for valid statistical interpretations.

Results

Survival. The median ages at death in the proton and cobalt controls were 845 and 825 days respectively. This agrees with control data in Fischer rats published by the National Institute of Environmental Health Sciences National Toxicology Program (NTP) /8/. The high early mortality in the 18-Gy-proton group was primarily attributable to respiratory complications associated with squamous metaplasia of the nasopharynx. This condition was infrequently seen in lower dose groups, where it was never identified as a factor in the animal's death. Similar early mortality was observed in the 18-Gy cobalt group; however, the lesions differed from those in the 18-Gy-proton group. The cobalt subjects did not develop obstructive squamous metaplasia of the nasopharynx, but instead had stomatitis, gingivitis, and malocclusion, resulting in severe malnutrition. Feeding finely crushed food pellets did little to alter the decline of these subjects. Survival data for all groups are given in Table 1 and Figures 3 and 4.

Table 1. Survival (Weeks) of Male F-344 Rats after Head-Only Irradiation

Dose	* Number of Subjects		Mean Survival Time		Median Survival Time		Total Weeks at Risk	
	Proton	Cobalt	Proton	Cobalt	Proton	Cobalt	Proton	Cobalt
0.0 Gy	221	61	104.4	107.9	110.7	114.6	23270	6659
2.0 Gy	196	40	97.3	109.1	101.8	113.7	20060	4366
4.0 Gy	163	40	96.8	94.7	99.9	96.6	15671	3786
8.5 Gy	195	37	90.0	85.9	91.3	86.7	17818	3092
18.0 Gy	156	38	39.0	28.7	33.6	21.0	5582	1088

* Different from the total number of rats exposed because data from some of the exposed subjects was unobtainable (see Data Analysis). Additional control data came from unused disease control sentinels.

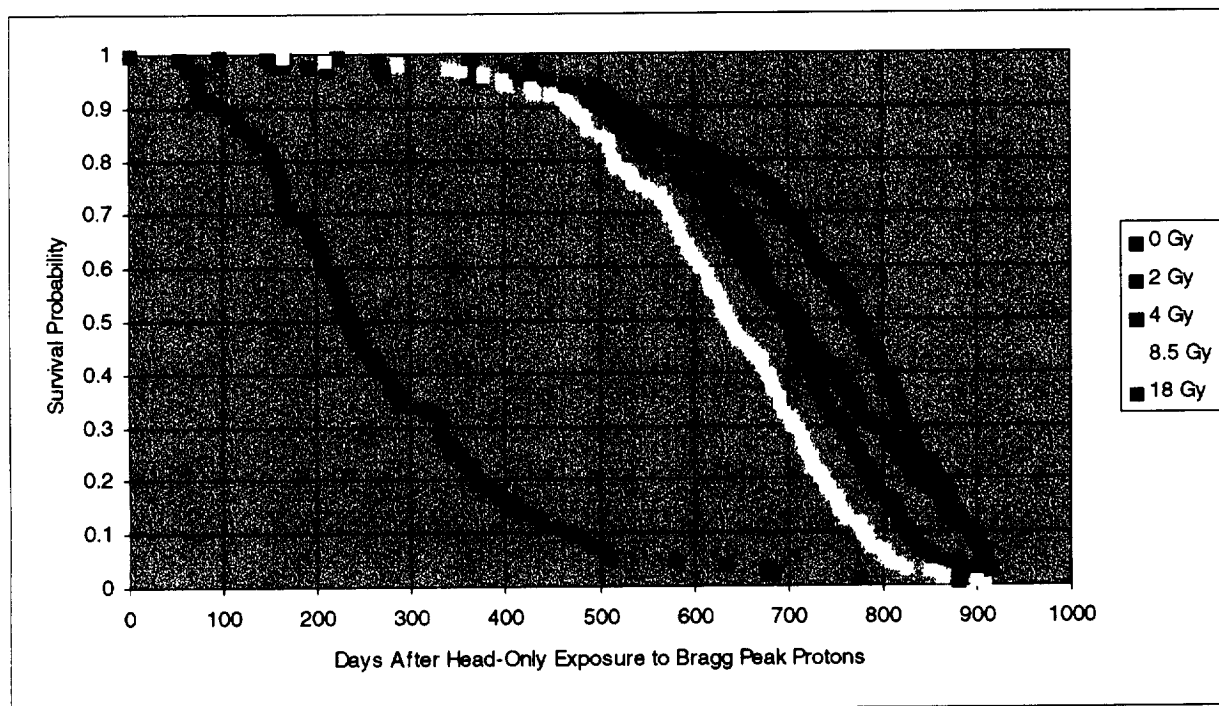


Figure 3. Kaplan-Meier survival probability of male F-344 rats after head-only exposure to Bragg Peak protons.

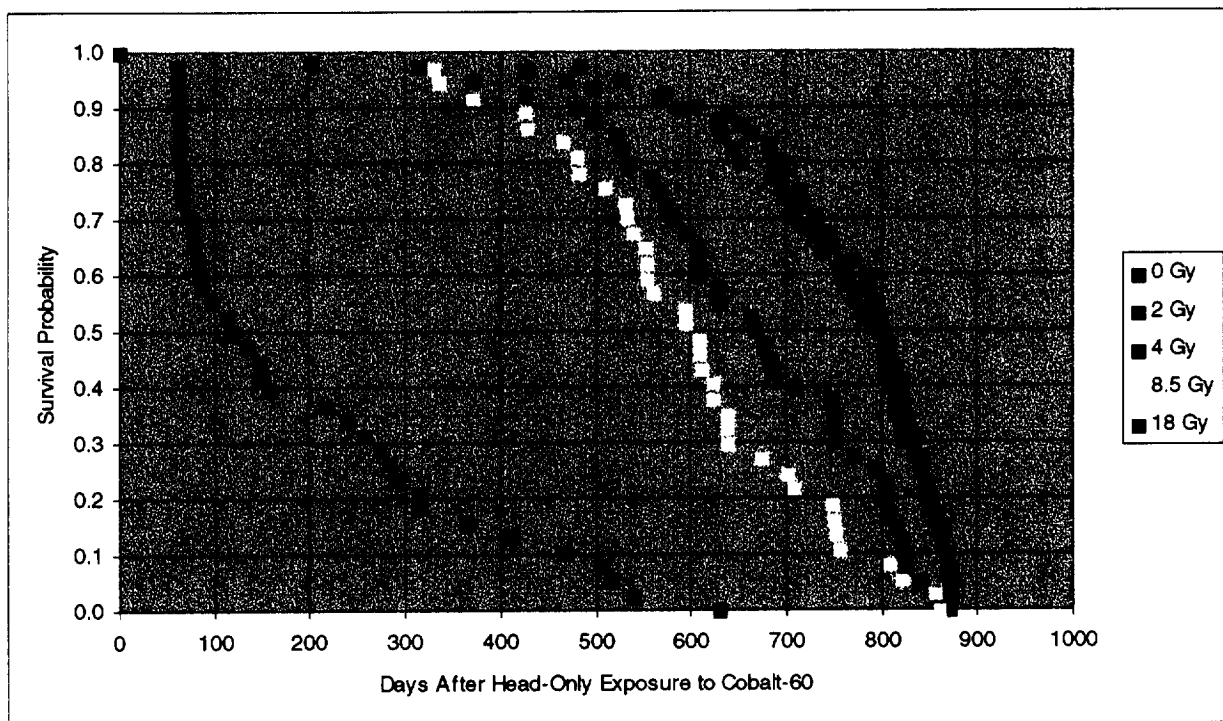


Figure 4. Kaplan-Meier survival probability of male F-344 rats after head-only exposure to ^{60}Co γ -radiation

The high early mortality in the 18-Gy groups undoubtedly precluded the expression of many tumors with long latent periods. Squamous metaplasia of the nasopharynx rarely occurs spontaneously, but is commonly seen as a response to chronically inhaled irritants. It is regarded as pre-cancerous and might develop into squamous cell carcinoma [8].

Solid Tumors. For both proton and cobalt irradiation, there was a dose-ordered incidence of total head and neck tumors that displayed a high degree of linearity, if data from the 18-Gy group were excluded from the regression (Figure 5). The slope of the regression line for protons predicts that the dose that would be required to double the naturally occurring number of all tumors of the head and neck would be 4.7 Gy. The correlation coefficient ($r = 0.9960$) indicates that the slope was very significantly different from zero. Similarly, the doubling dose of ^{60}Co γ -radiation was estimated to be 2.4 Gy ($r = 0.9944$). When only tumors of the brain and meninges were considered, the proton data indicated that the dose required to double the naturally occurring incidence would be 7.9 Gy; however, the correlation coefficient was not sufficient ($r = 0.8508$) to conclude that the slope was not zero. Similarly, the cobalt data showed even greater scatter ($r = 0.2906$); therefore, when only brain and meningeal tumors were considered, the data

were inconclusive.

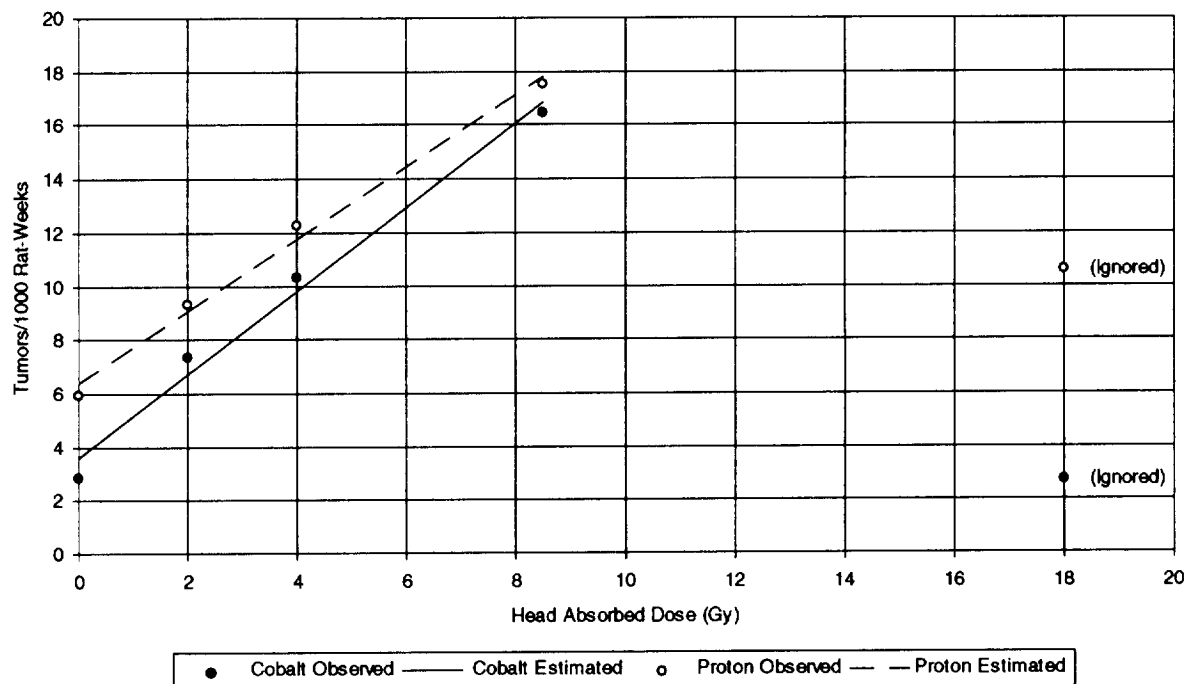


Figure 5 Incidence density plot of all head and neck tumors by dose group. Linear regressions exclude 18 Gy points.

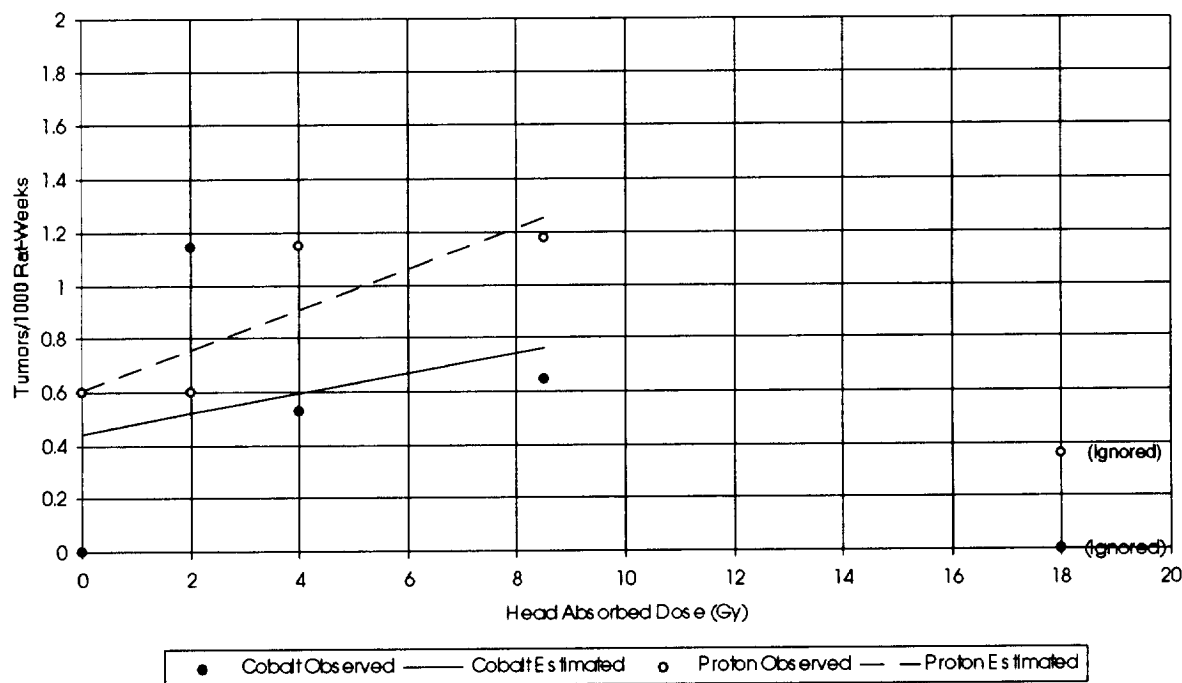


Figure 6. Incidence density plot of brain tumors by dose group. Linear regression excludes the 18 Gy points.

When the tumors were grouped by cell type, significant increases in the incidence of all

categories, especially pituitary chromophobe adenomas, epithelial cell, and mesenchymal cell tumors, were identified by χ^2 testing (Figure 7).

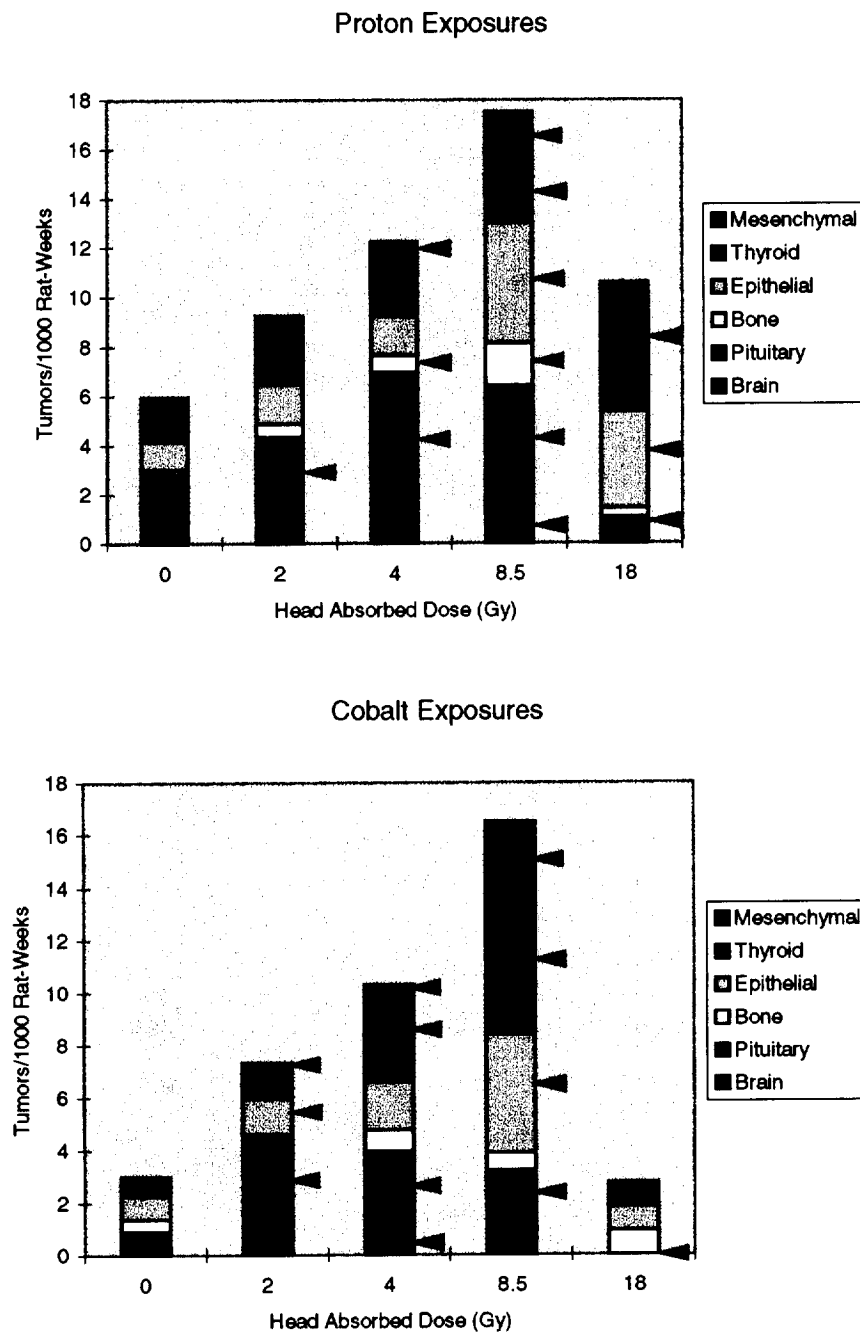


Figure 7. Life span incidence of head and neck tumors by primary cell type. Black arrows mark values that are significant (outside the 95th percentile of the χ^2 distribution with 1 d.f. when comparing incidence density in experimental groups with that of controls). Red arrows indicate values that are significantly less than corresponding control values.

Leukemia. Aging Fischer rats have a high incidence of fatal mononuclear cell leukemia (MCL), which accounted for many of the deaths in all groups, including the controls. The natural incidence of MCL in male rats is reported to be approximately 30% /10/. The data upon which this is based are primarily from 2-year carcinogenesis studies; therefore, the figure might be slightly higher in subjects such as ours that are allowed to complete their entire life span. MCL is seldom seen in rats that die before 16 months of age, but it is the cause of 50% of the naturally occurring deaths in Fischer rats under 20 months of age /10/. The incidence in our study is shown in Figure 8.

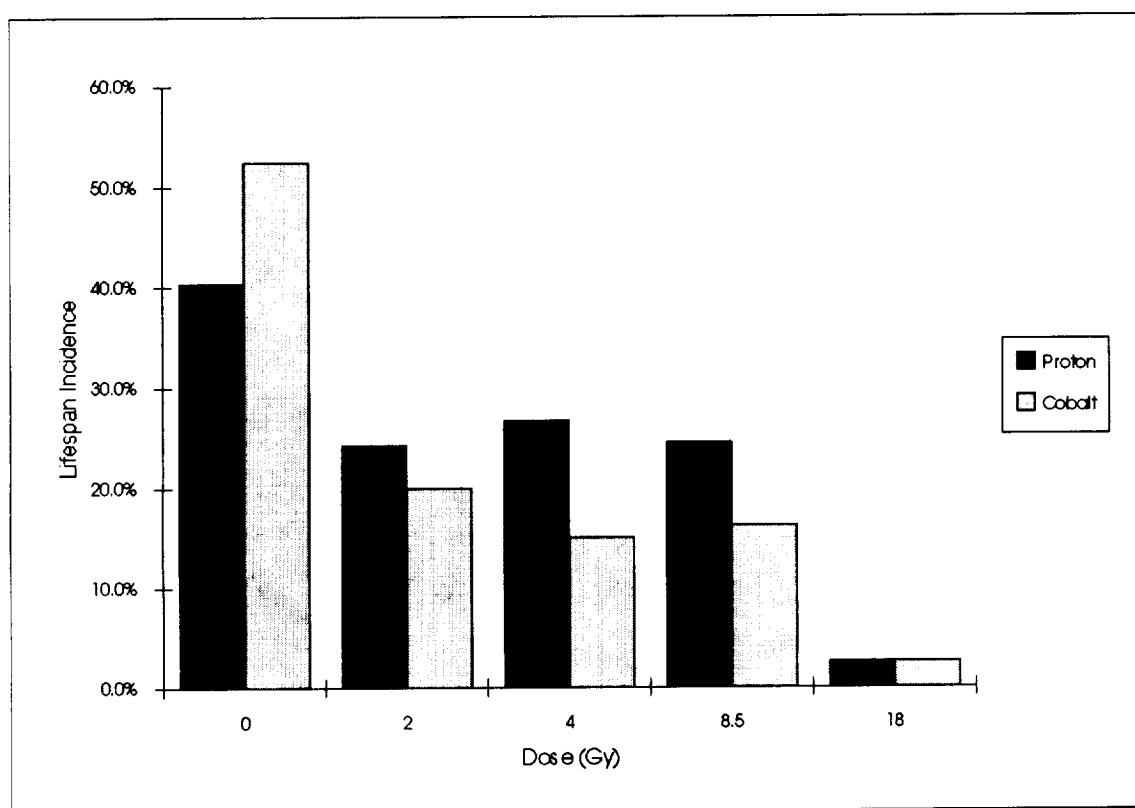


Figure 8. Life span incidence of mononuclear cell leukemia in rats exposed to head-only proton or ^{60}Co γ irradiation.

For either radiation type, the lifetime incidence was directly related to the average longevity of the subjects, irrespective of the dose of radiation that was absorbed by the head.

Discussion and Conclusions

The combined incidence of all head and neck tumors in irradiated rats was significantly greater than that in the controls in every exposure group except the high dose Cobalt exposures. Most of these tumors were identified on post-mortem examination and were not the primary cause of death. Pituitary adenomas accounted for the greater part of this increase in the 2 and 4-Gy groups, while epithelial and mesenchymal cell tumors were more prevalent in the 8.5 and 18-Gy groups. The 18-Gy-proton group had a significantly lower incidence of pituitary tumors than the controls, probably because of the high mortality from other causes during the latent period of the tumor. There was no relationship between the exposure to energetic protons and the occurrence of malignant gliomas of the type that was seen in proton-irradiated monkeys. The life span incidence of brain tumors (all types) in the proton control group was 6.3 % (14/221), compared with 1.04 % (20/1928), in the NTP control rats that were sacrificed at the two-year point /8/. At the two-year point in the proton study, the control rats had accumulated 21290 rat-weeks at risk, while the end of the experiment the total was 23270. The additional 1980 weeks at risk in elderly rats might, at least in part, account for the observed five-fold difference in brain tumor incidence between the two-year and life span control subjects. It is also possible that the serial sectioning technique employed by the pathologist in locating microscopic tumors resulted in a high efficiency of identification. The only experimental group that had a significantly higher brain tumor incidence than the controls was the 8.5-Gy-proton group, which also had significantly higher incidence in every category of tumor. Referring to Figure 7, the largest percentage increase in any type of tumor in the 8.5-Gy-proton group was in bone tumors (8.3 x control), while the smallest was in thyroid tumors (1.7 x control). The increases in brain and pituitary tumors were nearly the same (2.0 and 2.4 x control), while the increases in miscellaneous epithelial and mesenchymal cell tumors were slightly higher (4.2 and 5.2 x control). We conclude that the thyroid, brain and pituitary would be among the least sensitive of the tissues of the head and neck to the carcinogenic effects of high energy protons, while the epithelium, and all mesenchymal tissues including bone would be the most vulnerable. Regarding the high incidence malignant gliomas in proton-irradiated monkeys, the evidence suggests that the effect is related to the unequal dose distribution of the 55-MeV protons, and that the tumors probably were initiated

in those areas that received considerably more than the measured surface dose.

Irradiation of the head did not cause an increase in the incidence of leukemia. This might be attributable to the fact that most blood forming tissues were excluded from the radiation field; however, in studies by others, the rate of MCL has also shown a similar lack of response to orally administered chemical carcinogens /11/. Our data agree with the hypothesis that MCL risk is related to age and is independent of radiation dose to the head. We conclude that, although leukemia was a significant cause of mortality, it was not a confounding factor in the interpretation of solid tumor data.

The fact that both 18-Gy groups had similar mortality patterns but dissimilar lesions related to that mortality was an intriguing puzzle. It appears reasonable to suggest that the damage at the macromolecular level that is caused by Bragg Peak Protons is different from damage caused by ^{60}Co γ -photons.

We conclude that, based on a rat model, the RBE of Bragg Peak protons for the induction of all types of head and neck tumors combined is not significantly different from unity. The attempt to extend the dose-response curve in rats to 18 Gy was not a success due to the debilitating subacute effects in the rats at this dose of either cobalt or proton radiation. The early deaths of these subjects limited the usefulness of the rodent model in assessing the risk of the specific type of malignant tumor (glioblastoma) that occurred in the proton-exposed monkeys because of the relatively long latent period of radiation-induced neural tumors. Nevertheless, the similar incidence densities of all types of tumors combined at all doses in the range of 2 - 8.5 Gy suggests that equal absorbed doses of cobalt and solar proton radiation will result in similar risk of neural tumors in species that have a longer life span than rats.

During extended space travel, such as a manned mission to Mars, adequate radiation risk assessment will depend on having an accurate record of the energy spectrum of the solar protons that contribute to the measured surface absorbed dose. Because of the unequal dose distribution along the path of those protons that have insufficient energy to pass completely through the head, the risk of brain tumors will depend on the amount of energy absorbed at the site of radiation-sensitive tissues.

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File No	Dose	Died	Brain	Pituitary	Bone	Epithelial	Thyroid	Mesenchymal	All H&N	Metaplasia
All			67	313	60	195	149	107	891	73
894016	0	13-Dec-89							0	
894031	0	15-Dec-89							0	
900092	0	19-Dec-89				1			1	
900187	0	15-Feb-90	1						1	
900523	0	17-Apr-90							0	
900901	0	19-Jul-90							0	
901009	0	31-Jul-90				1			1	
901340	0	9-Sep-90	1						1	
901427	0	26-Sep-90							0	
901466	0	26-Sep-90							0	
901596	0	29-Oct-90							0	
901730	0	20-Nov-90							0	
901733	0	20-Nov-90							0	
901808	0	26-Nov-90							0	
901844	0	30-Nov-90							0	
901869	0	17-Dec-90	1						1	
901876	0	17-Dec-90							0	
902010	0	19-Dec-90							0	
902011	0	19-Dec-90							0	
902028	0	21-Dec-90				1			1	
902035	0	28-Dec-90				1			1	
910001	0	4-Jan-91						1	1	
910002	0	4-Jan-91				1			1	
910004	0	7-Jan-91		1	1				2	
910022	0	10-Jan-91							0	
910083	0	18-Jan-91	1				1		2	
910090	0	23-Jan-91							0	1
910182	0	1 Feb 91							0	
910210	0	14 Feb-91							0	
910490	0	15-Feb-91							0	
910509	0	4-Mar-91	1			1			2	
910510	0	11-Mar-91							0	
910824	0	11-Mar-91							0	
910836	0	11-Mar-91							0	
910960	0	27-Mar-91							0	
910987	0	3-Apr-91		1					1	
911002	0	1-Apr-91							0	
911049	0	9-Apr-91							0	
911050	0	9-Apr-91			1				1	
911055	0	11-Apr-91							0	
911083	0	16-Apr-91							0	
911091	0	18-Apr-91							0	
911225	0	1-May-91							0	
911287	0	9-May-91				1	1		2	
911288	0	9-May-91				1			1	
911291	0	10-May-91				1			1	
911366	0	24-May-91							0	
911463	0	31-May-91							0	
911464	0	31-May-91							0	
911466	0	31-May-91							0	
911467	0	1-Jun-91							0	
911469	0	3-Jun-91							0	
911481	0	5-Jun-91				2			2	
911495	0	6-Jun-91					1		1	
911500	0	7-Jun-91							0	
911502	0	7-Jun-91							0	
911504	0	10-Jun-91		1		1			2	
911505	0	10-Jun-91						1	1	
911506	0	10-Jun-91							0	
911539	0	12-Jun-91							0	
911544	0	13-Jun-91		1					1	

File No	Dose	Died	Brain	Pituitary	Bone	Epithelial	Thyroid	Mesenchymal	All H&N	Metaplasia
911546	0	13-Jun-91	1						1	
911588	0	17-Jun-91							0	
911591	0	17-Jun-91							0	
911597	0	18-Jun-91						1	1	
911692	0	21-Jun-91							0	
911701	0	25-Jun-91					1		1	
911950	0	1-Jul-91							0	
911953	0	1-Jul-91				1			1	
911978	0	2-Jul-91							0	
911988	0	5-Jul-91	1	1					2	
911989	0	5-Jul-91							0	
911996	0	8-Jul-91							0	
912078	0	10-Jul-91							0	
912079	0	10-Jul-91		1		1			2	
912148	0	12-Jul-91		1					1	
912157	0	15-Jul-91		1					1	
912158	0	16-Jul-91		1			1		2	
912160	0	16-Jul-91							0	
912168	0	17-Jul-91		1	1				2	
912169	0	17-Jul-91							0	
912170	0	17-Jul-91							0	
912178	0	19-Jul-91							0	
912181	0	22-Jul-92		1					1	
912185	0	22-Jul-91			1				1	
912186	0	22-Jul-91							0	
912249	0	26-Jul-91							0	
912251	0	26-Jul-91							0	
912257	0	29-Jul-91							0	
912308	0	1-Aug-91		1	1				2	
912330	0	7-Aug-91							0	
912337	0	7-Aug-91	1	2			1		4	
912345	0	13-Aug-91							0	
912349	0	13-Aug-91							0	
912350	0	13-Aug-91							0	
912351	0	13-Aug-91							0	
912353	0	13-Aug-91		1					1	
912510	0	20-Aug-91					1		1	
912519	0	22-Aug-91	1				1		2	
912522	0	23-Aug-91		1					1	
912526	0	26-Aug-91		1			1		2	
912528	0	26-Aug-91							0	
912530	0	27-Aug-91							0	
912600	0	28-Aug-91							0	
912614	0	29-Aug-91							0	
912616	0	29-Aug-91							0	
912622	0	30-Aug-91							0	
912624	0	3-Sep-91		1			1	1	3	
912626	0	3-Sep-91		1				1	2	
912820	0	5-Sep-91		1					1	
912833	0	6-Sep-91							0	
912836	0	9-Sep-91				1			1	
912837	0	9-Sep-91				1			1	
912841	0	9-Sep-91							0	
912957	0	10-Sep-91		1					1	
912959	0	10-Sep-91							0	
912963	0	11-Sep-91							0	
912964	0	11-Sep-91		1		1			2	
912980	0	16-Sep-91					1		1	
912984	0	17-Sep-91		1			1		2	
913032	0	22-Sep-91		1					1	
913033	0	24-Sep-91							0	
913034	0	24-Sep-91							0	

File No	Dose	Died	Brain	Pituitary	Bone	Epithelial	Thyroid	Mesenchymal	All H&N	Metaplasia
913035	0	24-Sep-91					1		1	
913036	0	24-Sep-91							0	
913050	0	26-Sep-91							0	
913051	0	26-Sep-91					1		1	
913055	0	27-Sep-91							0	
913118	0	1-Oct-91							0	
913120	0	1-Oct-91		1					1	
913121	0	1-Oct-91				1		1	2	
913130	0	4-Oct-91						1	1	
913133	0	6-Oct-91							0	
913134	0	5-Oct-91							0	
913137	0	7-Oct-91							0	
913139	0	7-Oct-91					1		1	
913141	0	8-Oct-91		1					1	
913154	0	10-Oct-91		1					1	
913157	0	11-Oct-91		1					1	
913159	0	11-Oct-91							0	
913160	0	14-Oct-91							0	
913161	0	15-Oct-91		1			1		2	
913165	0	15-Oct-91							0	
913168	0	16-Oct-91							0	
913171	0	17-Oct-91							0	
913172	0	17-Oct-91		1					1	
913173	0	17-Oct-91	1						1	
913176	0	18-Oct-91							0	
913177	0	20-Oct-91		1					1	
913178	0	21-Oct-91		1			1		2	
913179	0	21-Oct-91							0	
913181	0	21-Oct-91		1			1		2	
913345	0	28-Oct-91						1	1	
913346	0	28-Oct-91		1					1	
913348	0	28-Oct-91							0	
913349	0	29-Oct-91							0	
913350	0	29-Oct-91							0	
913352	0	29-Oct-91		1					1	
913354	0	30-Oct-91							0	
913356	0	31-Oct-91				1			1	
913361	0	1-Nov-91	1	1			1		3	
913362	0	1-Nov-91		1		1			2	
913367	0	4-Nov-91							0	
913368	0	4-Nov-91		1					1	
913384	0	6-Nov-91							0	
913386	0	6-Nov-91							0	
913499	0	7-Nov-91						1	1	
913515	0	19-Nov-91							0	
913522	0	19-Nov-91							0	
913523	0	20-Nov-91				1			1	
913527	0	21-Nov-91	1						1	
913528	0	21-Nov-91							0	
913530	0	21-Nov-91		1					1	
913579	0	22-Nov-91		1					1	
913580	0	22-Nov-91							0	
913582	0	25-Nov-91							0	
913585	0	26-Nov-91							0	
913588	0	29-Nov-91				1			1	
913678	0	3-Dec-91		1					1	
913690	0	4-Dec-91							0	
913691	0	5-Dec-91							0	
913694	0	6-Dec-91		1		1			2	
913698	0	7-Dec-91					1		1	
913699	0	8-Dec-91							0	
913700	0	9-Dec-91		1					1	

File No	Dose	Died	Brain	Pituitary	Bone	Epithelial	Thyroid	Mesenchymal	All H&N	Metaplasia
913701	0	9-Dec-91							0	
913790	0	13-Dec-91					1		1	
913792	0	14-Dec-91		1					1	
913804	0	15-Dec-91				2			2	
913805	0	15-Dec-91							0	
913825	0	16-Dec-91	1						1	
913827	0	17-Dec-91					1		1	
913828	0	17-Dec-91							0	
913833	0	18-Dec-91							0	
913868	0	24-Dec-91							0	
913869	0	24-Dec-91							0	
913895	0	30-Dec-91							0	
920006	0	6-Jan-92					1		1	
920008	0	6-Jan-92		1		1			2	
920071	0	7-Jan-92		1				1	2	
920089	0	8-Jan-92		1			1		2	
920129	0	9-Jan-92					1		1	
920132	0	9-Jan-92							0	
920135	0	10-Jan-92							0	
920138	0	10-Jan-92							0	
920142	0	10-Jan-92							0	
920227	0	15-Jan-92					1		1	
920228	0	15-Jan-92		1		1	1		3	
920285	0	23-Jan-92							0	
920287	0	22-Jan-92					1		1	
920289	0	27-Jan-92							0	
920293	0	28-Jan-92							0	
920294	0	28-Jan-92					2		2	
920295	0	28-Jan-92		1					1	
920306	0	30-Jan-92		1			1		2	
920307	0	30-Jan-92							0	
920309	0	30-Jan-92	1	1					2	
920311	0	30-Jan-92							0	
920314	0	31-Jan-92							0	
920315	0	31-Jan-92							0	
920316	0	31-Jan-92					1		1	
900236	2	28-Feb-90	1						1	
900555	2	3-May-90				1			1	
900905	2	19-Jul-90					1		1	
901462	2	26-Sep-90							0	
901463	2	26-Sep-90							0	
901464	2	26-Sep-90							0	
901468	2	26-Sep-90							0	
901599	2	30-Oct-90							0	
901706	2	7-Nov-90				1			1	
901810	2	28-Nov-90							0	
901846	2	4-Dec-90							0	
901854	2	10-Dec-90							0	
901856	2	10-Dec-90		1					1	
901865	2	14-Dec-90				1			1	
901868	2	15-Dec-90							0	
902013	2	19-Dec-90				1			1	
902033	2	25-Dec-90							0	
902038	2	31-Dec-90							0	
910019	2	10-Jan-91						1	1	
910020	2	10-Jan-91	1						1	
910027	2	14-Jan-91				1			1	
910085	2	18-Jan-91							0	
910089	2	23-Jan-91							0	
910091	2	30-Jan-91							0	
910134	2	4-Feb-91							0	
910208	2	7-Feb-91							0	

File No	Dose	Died	Brain	Pituitary	Bone	Epithelial	Thyroid	Mesenchymal	All H&N	Metaplasia
910213	2	14-Feb-91	1						1	
910466	2	17-Feb-91				1	1		2	
910493	2	25-Feb-91							0	
910512	2	11-Mar-91							0	
910536	2	12-Mar-91							0	
910838	2	13-Mar-91	1	1				1	3	
910840	2	14-Mar-91				1			1	
910853	2	15-Mar-91	1						1	
910854	2	15-Mar-91		1					1	
910855	2	15-Mar-91						1	1	
910858	2	18-Mar-91							0	
910930	2	20-Mar-91		1					1	
910958	2	22-Mar-91							0	
910983	2	2-Apr-91							0	
910986	2	3-Apr-91							0	
910989	2	3-Apr-91							0	
910990	2	3-Apr-91					2		2	
911029	2	4-Apr-91							0	
911039	2	6-Apr-91		1					1	
911052	2	10-Apr-91							0	
911054	2	11-Apr-91							0	
911071	2	12-Apr-91		1		1			2	
911073	2	12-Apr-91		1					1	
911079	2	16-Apr-91		1					1	
911081	2	16-Apr-91		1				1	2	
911085	2	17-Apr-91		1					1	
911088	2	17-Apr-91				1			1	
911089	2	18-Apr-91				1			1	
911101	2	22-Apr-91							0	
911183	2	26-Apr-91				1		1	2	
911184	2	26-Apr-91		1					1	
911219	2	29-Apr-91		1					1	
911221	2	29-Apr-91							0	
911226	2	1-May-91				1			1	
911262	2	6-May-91						1	1	
911289	2	9-May-91							0	
911293	2	13-May-91				1			1	
911294	2	13-May-91				1			1	
911295	2	13-May-91		1			1	1	3	
911297	2	13-May-91							0	
911321	2	17-May-91		1			1	1	3	
911322	2	17-May-91							0	
911324	2	20-May-91		1			2		3	
911325	2	20-May-91		1			1	1	3	
911326	2	20-May-91			1	1		1	3	
911327	2	20-May-91		1					1	
911328	2	20-May-91		1	1	1			3	
911329	2	20-May-91		1					1	
911334	2	22-May-91	1	1					2	
911335	2	22-May-91					1		1	
911336	2	22-May-91					1		1	
911351	2	23-May-91			1				1	
911371	2	25-May-91					1		1	
911372	2	28-May-91							0	
911373	2	28-May-91		1			1	1	3	
911374	2	28-May-91							0	
911376	2	28-May-91							0	
911377	2	28-May-91							0	
911381	2	29-May-91		1					1	1
911449	2	30-May-91		1					1	
911453	2	30-May-91							0	
911470	2	3-Jun-91				1			1	

File No	Dose	Died	Brain	Pituitary	Bone	Epithelial	Thyroid	Mesenchymal	All H&N	Metaplasia
911482	2	5-Jun-91	1						1	
911503	2	9-Jun-91	1						1	
911596	2	18-Jun-91				1			1	
911698	2	24-Jun-91			1				1	
911699	2	24-Jun-91			1				1	
911947	2	28-Jun-91		1					1	
911948	2	28-Jun-91							0	
911951	2	1-Jul-91		1					1	
911985	2	5-Jul-91		1					1	
911993	2	8-Jul-91							0	
911997	2	8-Jul-91						1	1	
911998	2	8-Jul-91		1					1	
911999	2	8-Jul-91		1					1	
912000	2	9-Jul-91		1		1	1		3	
912001	2	9-Jul-91				1		1	2	
912003	2	9-Jul-91							0	
912076	2	10-Jul-91						1	1	
912151	2	12-Jul-91							0	
912154	2	15-Jul-91		1					1	
912179	2	23-Jul-92							0	
912183	2	23-Jul-92							0	
912252	2	26-Jul-91		1					1	
912253	2	26-Jul-91		1					1	
912256	2	29-Jul-91							0	
912306	2	1-Aug-91		1					1	
912340	2	11-Aug-91		1					1	
912343	2	12-Aug-91		1					1	
912348	2	13-Aug-91		1					1	
912494	2	7-Aug-91			1				1	
912496	2	15-Aug-91		1					1	
912497	2	15-Aug-91		1					1	
912504	2	19-Aug-91			1				1	
912505	2	19-Aug-91		1			1		2	
912509	2	20-Aug-91					1		1	
912525	2	26-Aug-91				1			1	
912527	2	26-Aug-91					1		1	
912532	2	27-Aug-91		1					1	
912617	2	29-Aug-91				1	1		2	
912618	2	29-Aug-91					1		1	
912623	2	30-Aug-91		1				1	2	
912628	2	3-Sep-91		1					1	
912829	2	6-Sep-91							0	
912831	2	6-Sep-91		1					1	
912968	2	12-Sep-91					1		1	
912969	2	12-Sep-91							0	
912970	2	12-Sep-91		1					1	
912978	2	16-Sep-91		1		1			2	
913031	2	21-Sep-91		1					1	
913042	2	25-Sep-91		2					2	
913114	2	1-Oct-91			1		1		2	
913131	2	4-Oct-91		1		2			3	
913136	2	7-Oct-91		1					1	
913149	2	9-Oct-91		1					1	
913150	2	9-Oct-91		1					1	
913153	2	10-Oct-91		1			1		2	
913155	2	10-Oct-91		1			1		2	
913164	2	15-Oct-91							0	
913174	2	17-Oct-91		1					1	
913182	2	21-Oct-91			1				1	
913335	2	23-Oct-91							0	
913336	2	23-Oct-91					1	1	2	
913344	2	28-Oct-91							0	

File No	Dose	Died	Brain	Pituitary	Bone	Epithelial	Thyroid	Mesenchymal	All H&N	Metaplasia
913351	2	29-Oct-91					1		1	
913355	2	30-Oct-91							0	
913357	2	31-Oct-91							0	
913358	2	31-Oct-91		1					1	
913359	2	31-Oct-91		1			2		3	
913363	2	4-Nov-91							0	
913500	2	8-Nov-91	1			1	1		3	
913503	2	12-Nov-91					1		1	
913512	2	18-Nov-91					1		1	
913529	2	21-Nov-91		1					1	
913584	2	24-Nov-91		1			1		2	
913587	2	29-Nov-91					1		1	
913676	2	2-Dec-91				1			1	
913677	2	3-Dec-91					1		1	
913692	2	5-Dec-91				1			1	
913693	2	5-Dec-91							0	
913695	2	6-Dec-91		1					1	
913696	2	6-Dec-91				1			1	
913697	2	00-Dec-91					1		1	
913791	2	6-Dec-91	1						1	
913793	2	7-Dec-91							0	
913803	2	8-Dec-91							0	
913831	2	17-Dec-91		1		1	1		3	
913870	2	24-Dec-91		1					1	
914007	2	31-Dec-91		1					1	
920003	2	5-Jan-92		1					1	
920005	2	5-Jan-92	1	1		1			3	
920072	2	7-Jan-92							0	
920088	2	8-Jan-92		1					1	
920128	2	9-Jan-92		1					1	
920133	2	10-Jan-92		1					1	
920134	2	10-Jan-92							0	
920136	2	10-Jan-92		1			1		2	
920137	2	10-Jan-92		1				1	2	
920140	2	10-Jan-92			1				1	
920240	2	17-Jan-92							0	
920241	2	17-Jan-92		1	1				2	
920274	2	22-Jan-92		1		1	1		3	
920275	2	22-Jan-92							0	
920276	2	22-Jan-92		1					1	
920286	2	22-Jan-92							0	
920288	2	27-Jan-92	1				1		2	
920290	2	27-Jan-92		1					1	
920310	2	30-Jan-92							0	
920317	2	31-Jan-92		1					1	
920318	2	31-Jan-92					1		1	
900006	4	4-Jan-90							0	
900512	4	12-Apr-90							0	
900834	4	18-Jul-90							0	
900904	4	19-Jul-90	1						1	
901022	4	2-Aug-90		1					1	
901245	4	25-Aug-90		1					1	
901345	4	11-Sep-90							0	
901407	4	21-Sep-90	1						1	
901410	4	24-Jul-90				1			1	
901426	4	26-Sep-90							0	
901467	4	27-Sep-90							0	
901485	4	8-Oct-90	1						1	
901600	4	31-Oct-90	1	1					2	
901603	4	3-Nov-90		1					1	
901737	4	21-Nov-90		1					1	
901809	4	28-Nov-90							0	

File No	Dose	Died	Brain	Pituitary	Bone	Epithelial	Thyroid	Mesenchymal	All H&N	Metaplasia
901843	4	30-Nov-90							0	
901847	4	6-Dec-90						1	1	
901862	4	14-Dec-90		1			1		2	
901874	4	17-Dec-90		1		1			2	
902007	4	19-Dec-90		1					1	
902029	4	24-Dec-90		1					1	
902030	4	24-Dec-90		1					1	
902031	4	24-Dec-90		1		1			2	
902037	4	31-Dec-90		1		1			2	
910025	4	12-Jan-91							0	
910026	4	14-Jan-91				1			1	
910041	4	17-Jan-91		1					1	
910082	4	18-Jan-91		1	1				2	
910084	4	18-Jan-91		1					1	
910087	4	19-Jan-91	1						1	
910088	4	19-Jan-91		1					1	
910207	4	22-Jan-91				1			1	
910209	4	31-Jan-91						1	1	
910519	4	1-Feb-91		1					1	
910542	4	21-Feb-91	1	1	1			1	4	
910823	4	26-Feb-91	1						1	
910832	4	1-Mar-91		1					1	
910834	4	7-Mar-91	1	1					2	
910857	4	17-Mar-91		1					1	
910956	4	22-Mar-91	1	1					2	
910967	4	28-Mar-91		1					1	
910976	4	29-Mar-91		1					1	
910979	4	29-Mar-91		1	1	1	1		4	
910982	4	2-Apr-91							0	
910985	4	3-Apr-91							0	
910988	4	3-Apr-91							0	
911027	4	4-Apr-91		1					1	
911028	4	4-Apr-91		1					1	
911030	4	4-Apr-91		1		1			2	
911031	4	4-Apr-91		1					1	
911041	4	8-Apr-91					1		1	
911080	4	16-Apr-91				1			1	
911090	4	18-Apr-91		1					1	
911097	4	19-Apr-91							0	
911098	4	20-Apr-91		1	1	1			3	
911099	4	22-Apr-91		1					1	
911174	4	25-Apr-91		1			1		2	
911175	4	25-Apr-91	1	1					2	
911185	4	26-Apr-91	1						1	
911264	4	6-May-91		1					1	
911285	4	9-May-91					1		1	
911290	4	9-May-91							0	
911292	4	12-May-91							0	
911296	4	13-May-91		1					1	
911305	4	16-May-91		1		1	1		3	
911333	4	22-May-91							0	
911352	4	23-May-91				1	1		2	
911353	4	23-May-91	1	1					2	
911380	4	28-May-91							0	
911452	4	30-May-91							0	
911465	4	31-May-91							0	
911480	4	5-Jun-91		1					1	
911499	4	7-Jun-91					1		1	
911589	4	17-Jun-91	1	1		1			3	
911594	4	7-Jun-91			1				1	
911595	4	18-Jun-91		1					1	
911598	4	18-Jun-91		1					1	

File No	Dose	Died	Brain	Pituitary	Bone	Epithelial	Thyroid	Mesenchymal	All H&N	Metaplasia
911603	4	20-Jun-91		1					1	
911691	4	21-Jun-91		1					1	
911693	4	21-Jun-91		1					1	
911694	4	21-Jun-91							0	
911697	4	24-Jun-91							0	
911700	4	24-Jun-91			1	1			2	
911703	4	25-Jun-91							0	
911707	4	26-Jun-91		1		1			2	
911708	4	26-Jun-91		1		1			2	
911724	4	27-Jun-91				1			1	
911979	4	2-Jul-91		1					1	
911980	4	2-Jul-91		1		1			2	
911981	4	3-Jul-91							0	
911983	4	4-Jul-91							0	
911995	4	8-Jul-91		1		1			2	
912077	4	10-Jul-91					1	1	2	
912152	4	13-Jul-91		1					1	
912155	4	15-Jul-91					1		1	
912161	4	16-Jul-91		1		1	1		3	
912166	4	17-Jul-91							0	
912182	4	22-Jul-92		1		1	1		3	
912184	4	22-Jul-92		1					1	
912190	4	24-Jul-91		1					1	
912191	4	24-Jul-91		1					1	
912192	4	24-Jul-91		1					1	
912248	4	26-Jul-91	1	1				1	3	
912250	4	26-Jul-91						1	1	
912259	4	30-Jul-91					1		1	
912322	4	2-Aug-91	1	1					2	
912323	4	2-Aug-91							0	
912331	4	7-Aug-91						1	1	
912332	4	7-Aug-91							0	
912334	4	7-Aug-91		1	1				2	
912341	4	10-Aug-91		1					1	
912495	4	15-Aug-91		1			1		2	
912500	4	16-Aug-91		1					1	
912502	4	18-Aug-91		1		1			2	
912506	4	19-Aug-91							0	
912514	4	21-Aug-91		1	1				2	
912531	4	27-Aug-91	1	1					2	
912533	4	27-Aug-91					1		1	
912613	4	29-Aug-91					1		1	
912615	4	29-Aug-91							0	
912627	4	3-Sep-91		1					1	
912821	4	5-Sep-91							0	
912828	4	6-Sep-91				1			1	
912835	4	8-Sep-91							0	
912838	4	9-Sep-91	1					1	2	
912840	4	9-Sep-91		1		1			2	
912958	4	10-Sep-91					1	1	2	
912974	4	13-Sep-91		1	1				2	
912977	4	16-Sep-91		1					1	
912979	4	16-Sep-91		1	1		2		4	
912983	4	17-Sep-91		1					1	
913030	4	21-Sep-91		1			1		2	
913052	4	26-Sep-91		1			1	1	3	
913053	4	26-Sep-91					1		1	
913054	4	26-Sep-91					1		1	
913128	4	4-Oct-91					1	1	2	
913138	4	7-Oct-91		1					1	
913152	4	10-Oct-91		1			2		3	
913156	4	11-Oct-91		1					1	

File No	Dose	Died	Brain	Pituitary	Bone	Epithelial	Thyroid	Mesenchymal	All H&N	Metaplasia
913158	4	11-Oct-91					1		1	
913163	4	15-Oct-91			1				1	
913166	4	16-Oct-91		1					1	
913167	4	16-Oct-91							0	
913169	4	16-Oct-91		1		1			2	
913180	4	21-Oct-91						1	1	
913333	4	23-Oct-91		1					1	
913347	4	28-Oct-91		1			1		2	
913353	4	29-Oct-91					1		1	
913360	4	1-Nov-91		1				1	2	
913385	4	6-Nov-91							0	
913387	4	6-Nov-91		1					1	
913501	4	8-Nov-91					1	1	2	
913510	4	15-Nov-91		1					1	
913586	4	29-Nov-91						1	1	
913824	4	16-Dec-91					1		1	
913829	4	17-Dec-91		1					1	
914006	4	31-Dec-91		1					1	
920009	4	6-Jan-92		1					1	
920139	4	10-Jan-92							0	
920141	4	10-Jan-92	1				1		2	
920296	4	28-Jan-92		1					1	
920308	4	30-Jan-93		1					1	
900194	8.5	18-Feb-90	1						1	
900544	8.5	3-May-90				1			1	
900553	8.5	3-May-90							0	
900554	8.5	3-May-90				1			1	
900669	8.5	26-Jul-90						1	1	
901019	8.5	1-Sep-90				1			1	
901020	8.5	1-Aug-90							0	
901023	8.5	2-Aug-90		1		1			2	
901228	8.5	23-Aug-90				1			1	
901230	8.5	24-Aug-90							0	
901232	8.5	26-Aug-90							0	
901246	8.5	25-Aug-90		1		1			2	
901408	8.5	21-Sep-90				1			1	
901409	8.5	24-Sep-90				1			1	
901491	8.5	12-Oct-90				1			1	
901505	8.5	22-Oct-90				1			1	
901580	8.5	25-Oct-90	1						1	
901595	8.5	26-Oct-90							0	
901598	8.5	30-Oct-90		1		1			2	
901601	8.5	2-Nov-90		1		1			2	
901604	8.5	4-Nov-90				1			1	
901704	8.5	7-Nov-90				1		1	2	
901717	8.5	12-Nov-90				1			1	
901718	8.5	13-Nov-90				1		1	2	
901725	8.5	19-Nov-90			1				1	
901731	8.5	20-Nov-90	1			1			2	
901732	8.5	20-Nov-90	2						2	
901734	8.5	20-Nov-90							0	
901736	8.5	21-Nov-90			1	1			2	
901848	8.5	6-Dec-90		1					1	
901849	8.5	6-Dec-90		1					1	
901859	8.5	13-Dec-90		1					1	
901860	8.5	13-Dec-90							0	
901863	8.5	14-Dec-90							0	
901866	8.5	14-Dec-90				1			1	
901870	8.5	17-Dec-90		1					1	
901871	8.5	17-Dec-90		1		1			2	
901872	8.5	17-Dec-90		1		1			2	
901873	8.5	17-Dec-90		1			1		2	

File No	Dose	Died	Brain	Pituitary	Bone	Epithelial	Thyroid	Mesenchymal	All H&N	Metaplasia
901875	8.5	17-Dec-90	1						1	
902009	8.5	19-Dec-90				1			1	
902012	8.5	19-Dec-90							0	
902027	8.5	21-Dec-90							0	
902039	8.5	31-Dec-90		1					1	
910003	8.5	4-Jan-91		1	1				2	
910005	8.5	7-Jan-91							0	
910006	8.5	7-Jan-91				2			2	
910007	8.5	7-Jan-81		1					1	
910018	8.5	10-Jan-91							0	
910086	8.5	18-Jan-91		1			1		2	
910184	8.5	26-Jan-91		1					1	
910214	8.5	27-Jan-91		1	1	2			4	
910465	8.5	4-Feb-91							0	
910467	8.5	4-Feb-91				1			1	
910468	8.5	4-Feb-91						1	1	
910491	8.5	7-Feb-91						1	1	
910492	8.5	7-Feb-91				1			1	
910508	8.5	10-Feb-91							0	
910511	8.5	14-Feb-91	1						1	
910513	8.5	15-Feb-91		1					1	
910517	8.5	16-Feb-91		1		1			2	
910518	8.5	16-Feb-91		1					1	
910520	8.5	18-Feb-91	1	1			1		3	
910541	8.5	21-Feb-91		1				1	2	
910543	8.5	26-Feb-91		1					1	
910624	8.5	28-Feb-91		1				1	2	
910625	8.5	6-Mar-91						1	1	
910626	8.5	6-Mar-91				1			1	
910627	8.5	6-Mar-91		1	1				2	
910825	8.5	7-Mar-91	1	1				1	3	
910833	8.5	7-Mar-91				1	1		2	
910835	8.5	7-Mar-91		1					1	
910837	8.5	7-Mar-91				1	1		2	
910839	8.5	11-Mar-91				1			1	
910845	8.5	14-Mar-91		1			1		2	
910852	8.5	15-Mar-91		1	1	1			3	
910931	8.5	20-Mar-91				1	1	1	3	
910932	8.5	20-Mar-91		1				1	2	
910957	8.5	22-Mar-91		1	1				2	
910959	8.5	27-Mar-91	1				1		2	
910968	8.5	28-Mar-91		1					1	
910969	8.5	28-Mar-91				1			1	
910977	8.5	29-Mar-91	1				1		2	
910978	8.5	29-Mar-91				1			1	
910981	8.5	1-Apr-91			1	1			2	
911040	8.5	6-Apr-91	1		1			1	3	
911048	8.5	9-Apr-91	1	1		1			3	
911051	8.5	9-Apr-91		1		1			2	
911056	8.5	11-Apr-91		1		1	1		3	
911057	8.5	11-Apr-91						1	1	
911058	8.5	11-Apr-91					1	1	2	
911070	8.5	12-Apr-91		1				1	2	
911072	8.5	12-Apr-91	1			2			3	
911084	8.5	16-Apr-91		1					1	
911086	8.5	17-Apr-91						1	1	
911087	8.5	17-Apr-91				1			1	
911100	8.5	22-Apr-91							0	
911102	8.5	22-Apr-91		1	1	1			3	
911176	8.5	25-Apr-91		1					1	
911177	8.5	25-Apr-91		1		1			2	
911178	8.5	25-Apr-91		1		1			2	

File No	Dose	Died	Brain	Pituitary	Bone	Epithelial	Thyroid	Mesenchymal	All H&N	Metaplasia
911186	8.5	26-Apr-91		1				1	2	
911220	8.5	29-Apr-91				1		1	2	
911224	8.5	1-May-91					1		1	
911263	8.5	6-May-91		1	1				2	
911286	8.5	9-May-91		1					1	
911299	8.5	14-May-91							0	
911306	8.5	16-May-91		1		3		1	5	
911307	8.5	16-May-91		1				1	2	
911350	8.5	23-May-91		1				1	2	
911367	8.5	24-May-91					1		1	
911368	8.5	24-May-91		1		1			2	
911450	8.5	30-May-91				2	1	1	4	
911451	8.5	30-May-91							0	
911454	8.5	30-May-91				1			1	
911468	8.5	1-Jun-91		1		2			3	
911471	8.5	3-Jun-91	1	1				1	3	
911472	8.5	3-Jun-91		1				1	2	
911473	8.5	3-Jun-91		1				1	2	
911492	8.5	6-Jun-91			1				1	
911494	8.5	6-Jun-91		1				1	2	
911498	8.5	7-Jun-91				1	1		2	
911501	8.5	7-Jun-91							0	
911537	8.5	12-Jun-91		1					1	
911538	8.5	12-Jun-91				1			1	
911540	8.5	12-Jun-91					1		1	
911543	8.5	13-Jun-91							0	
911545	8.5	13-Jun-91				1	1	1	3	
911587	8.5	17-Jun-91			1				1	
911590	8.5	17-Jun-91							0	
911592	8.5	17-Jun-91		1			2		3	
911593	8.5	17-Jun-91			1				1	
911696	8.5	23-Jun-91			1				1	
911702	8.5	25-Jun-91						1	1	
911704	8.5	25-Jun-91	1			2			3	
911709	8.5	26-Jun-91		1		2			3	
911710	8.5	26-Jun-91			1	2	2		5	
911725	8.5	27-Jun-91	1	1	1				3	
911952	8.5	1-Jul-91		1			1		2	
911984	8.5	5-Jul-91		1		1			2	
911986	8.5	5-Jul-91				1			1	
911987	8.5	5-Jul-91	1						1	
911990	8.5	6-Jul-91					1		1	
911992	8.5	8-Jul-91	1	1			1		3	
911994	8.5	8-Jul-91		1	1	1			3	
912002	8.5	9-Jul-91		1		1		1	3	
912149	8.5	12-Jul-91			1				1	
912150	8.5	12-Jul-91		1					1	
912156	8.5	15-Jul-91		1			1		2	
912159	8.5	16-Jul-91		1		1	1		3	
912162	8.5	16-Jul-91		1					1	
912167	8.5	17-Jul-91			1	1			2	
912180	8.5	22-Jul-92		1	2				3	
912189	8.5	24-Jul-91						1	1	
912243	8.5	25-Jul-91		1					1	
912255	8.5	28-Jul-91		1		1			2	
912258	8.5	30-Jul-91	1	1			1	1	4	
912260	8.5	30-Jul-91		1	1				2	
912307	8.5	1-Aug-91							0	
912333	8.5	7-Aug-91		1				1	2	
912335	8.5	7-Aug-91		1		1	1		3	
912336	8.5	7-Aug-91		1		1			2	
912342	8.5	10-Aug-91		1					1	

File No	Dose	Died	Brain	Pituitary	Bone	Epithelial	Thyroid	Mesenchymal	All H&N	Metaplasia
912344	8.5	10-Aug-91			1				1	
912352	8.5	13-Aug-91		1		1		1	3	
912372	8.5	14-Aug-91		1					1	
912373	8.5	14-Aug-91							0	
912498	8.5	14-Aug-91					1		1	
912507	8.5	19-Aug-91			1			2	3	
912515	8.5	21-Aug-91		1			1		2	
912520	8.5	22-Aug-91		1					1	
912625	8.5	3-Sep-91		1			1		2	
912807	8.5	4-Sep-91		1	1	1			3	
912832	8.5	6-Sep-91		1	1		1		3	
912834	8.5	7-Sep-91		1					1	
912839	8.5	9-Sep-91			1				1	
912967	8.5	12-Sep-91				2	1	1	4	
912972	8.5	13-Sep-91							0	
912973	8.5	13-Sep-91		1			1		2	
912981	8.5	17-Sep-91				1		1	2	
912982	8.5	17-Sep-91		1		1			2	
913056	8.5	27-Sep-91			1		1		2	
913119	8.5	1-Oct-91		1		1	1		3	
913127	8.5	4-Oct-91		1					1	
913129	8.5	4-Oct-91			1	2			3	
913140	8.5	7-Oct-91		1				1	2	
913162	8.5	15-Oct-91	1						1	
913334	8.5	23-Oct-91					1	1	2	
913516	8.5	19-Nov-91		1		1	1		3	
913583	8.5	25-Nov-91		1		1			2	
913589	8.5	1-Dec-91		1					1	
913675	8.5	2-Dec-91		1	1				2	
920007	8.5	6-Jan-92		1		1	1		3	
920226	8.5	15-Jan-92						1	1	
920292	8.5	28-Jan-92					1		1	
893195	18	14-Sep-89							0	1
893208	18	14-Sep-89							0	1
893209	18	14-Sep-89							0	1
893233	18	22-Sep-89							0	1
893234	18	22-Sep-89							0	1
893235	18	25-Sep-89							0	1
893849	18	2-Oct-89							0	
893850	18	2-Oct-89							0	
893853	18	2-Oct-89							0	1
893854	18	3-Oct-89							0	1
893855	18	3-Oct-89							0	1
893856	18	5-Oct-89							0	1
893867	18	13-Oct-89							0	1
893877	18	19-Oct-89							0	1
893878	18	23-Oct-89							0	1
893885	18	26-Oct-89							0	1
893886	18	27-Oct-89							0	1
893922	18	6-Nov-89							0	1
893926	18	7-Nov-89							0	1
893934	18	14-Nov-89							0	1
893935	18	14-Nov-89							0	
893936	18	14-Nov-89							0	1
893940	18	17-Nov-89							0	1
893946	18	29-Nov-89							0	1
893948	18	21-Nov-89							0	1
893969	18	7-Dec-89							0	1
893970	18	6-Dec-89							0	1
894038	18	18-Dec-89							0	
894039	18	18-Dec-89							0	
894040	18	12-Dec-89							0	

File No	Dose	Died	Brain	Pituitary	Bone	Epithelial	Thyroid	Mesenchymal	All H&N	Metaplasia
894042	18	20-Dec-89							0	1
894043	18	20-Dec-89				1			1	1
894044	18	20-Dec-89							0	1
894051	18	26-Dec-89							0	1
894052	18	26-Dec-89							0	1
894057	18	28-Dec-89				1			1	1
894058	18	28-Dec-89							0	1
894061	18	31-Dec-89							0	1
894062	18	31-Dec-89							0	
900001	18	1-Jan-90							0	
900003	18	2-Jan-90							0	1
900004	18	2-Jan-90							0	1
900005	18	3-Jan-90							0	1
900009	18	8-Jan-90							0	1
900010	18	8-Jan-90							0	1
900128	18	22-Jan-90							0	1
900129	18	22-Jan-90							0	1
900141	18	23-Jan-90							0	
900143	18	25-Jan-90							0	1
900162	18	29-Jan-90							0	1
900163	18	29-Jan-90							0	
900165	18	31-Jan-90				1			1	1
900166	18	31-Jan-90							0	1
900167	18	4-Feb-90							0	1
900170	18	7-Feb-90							0	
900171	18	7-Feb-90							0	1
900174	18	10-Feb-90							0	1
900175	18	11-Feb-90							0	
900176	18	9-Feb-90							0	
900178	18	13-Feb-90							0	1
900183	18	14-Feb-90							0	
900184	18	14-Feb-90							0	
900203	18	21-Feb-90							0	
900227	18	25-Feb-90							0	1
900228	18	24-Feb-90							0	
900237	18	28-Feb-90							0	1
900238	18	28-Feb-90							0	1
900257	18	1-Mar-90							0	
900263	18	5-Mar-90							0	
900264	18	5-Mar-90							0	
900265	18	5-Mar-90							0	1
900266	18	5-Mar-90							0	1
900273	18	7-Mar-90				1			1	
900277	18	13-Mar-90							0	1
900278	18	13-Mar-90							0	
900279	18	14-Mar-90							0	
900280	18	14-Mar-90							0	
900282	18	16-Mar-90							0	
900400	18	18-Mar-90							0	1
900401	18	19-Mar-90							0	
900402	18	30-Mar-90							0	1
900410	18	24-Mar-90				1			1	1
900456	18	27-Mar-90			1				1	
900457	18	27-Mar-90							0	
900458	18	27-Mar-90							0	
900467	18	4-Apr-90							0	1
900479	18	6-Apr-90				1			1	
900482	18	9-Apr-90							0	
900491	18	11-Apr-90							0	1
900513	18	13-Apr-90							0	1
900516	18	13-Apr-90							0	1
900530	18	20-Apr-90				1			1	

File No	Dose	Died	Brain	Pituitary	Bone	Epithelial	Thyroid	Mesenchymal	All H&N	Metaplasia
900534	18	25-Apr-90							0	1
900535	18	29-Apr-90							0	1
900536	18	25-Apr-90							0	
900537	18	15-Jan-90							0	1
900551	18	3-May-90				1			1	
900552	18	3-May-90				1			1	
900562	18	5-May-90							0	1
900563	18	5-May-90							0	
900564	18	4-May-90							0	1
900583	18	25-May-90				1			1	
900596	18	31-May-90							0	1
900638	18	31-May-90							0	1
900654	18	18-Jun-90					1		1	1
900655	18	9-Jun-90						1	1	
900656	18	19-Jun-90				1		1	2	
900657	18	19-Jul-90						1	1	
900658	18	19-Jun-90				1		1	2	
900659	18	19-Jun-90				1			1	
900660	18	20-Jun-90							0	
900668	18	25-Jun-90							0	1
900670	18	26-Jun-90							0	1
900671	18	26-Jun-90						1	1	
900756	18	30-Jun-90							0	
900771	18	9-Jul-90				1		1	2	
900772	18	9-Jul-90						1	1	
900778	18	10-Jul-90						1	1	
900824	18	18-Jul-90						1	1	
900835	18	18-Jul-90		1					1	
900902	18	19-Jul-90					1		1	
900913	18	24-Jul-90						1	1	
900947	18	26-Jul-90							0	
900948	18	26-Jul-90						1	1	
901021	18	2-Aug-90				1			1	
901028	18	8-Aug-90						1	1	
901029	18	8-Aug-90	1						1	
901097	18	15-Aug-90							0	
901208	18	21-Aug-90							0	
901244	18	25-Aug-90							0	
901247	18	29-Aug-90		1					1	
901250	18	3-Sep-90							0	
901251	18	3-Sep-90						1	1	
901346	18	12-Sep-90		1				1	2	
901423	18	27-Sep-90						1	1	1
901469	18	29-Sep-90							0	
901482	18	2-Oct-90	1						1	
901483	18	2-Oct-90						1	1	
901497	18	16-Oct-90						1	1	
901597	18	29-Oct-90							0	
901705	18	7-Nov-90			1			1	2	
901727	18	20-Nov-90				1			1	
901728	18	20-Nov-90				1		1	2	
901811	18	28-Nov-90						1	1	
901857	18	10-Dec-90						1	1	
901858	18	9-Dec-90							0	
901864	18	14-Dec-90				1		1	2	
901928	18	20-Dec-90						1	1	
902036	18	31-Dec-90				1			1	
910521	18	21-Feb-91							0	
911082	18	16-Apr-91						1	1	
911375	18	28-May-91				2	1	1	4	
911493	18	6-Jun-91				1			1	
912830	18	6-Sep-91		1					1	

File No	Dose	Died	Brain	Pituitary	Bone	Epithelial	Thyroid	Mesenchymal	All H&N	Metaplasia
913830	18	17-Dec-91					1		1	
920004	18	5-Jan-92							0	

File No.	Dose	Died	Brain	Pituitary	Bone	Epithelial	Thyroid	Mesenchymal	All H & N	Metaplasia
All			9	42	9	30	38	12	140	0
9	0	19-Aug-92			1				1	
74	0	9-Mar-93							0	
158	0	19-Oct-93							0	
170	0	2-Dec-93							0	
173	0	2-Dec-93							0	
174	0	2-Dec-93							0	
72	0	28-Dec-93							0	
8	0	7-Mar-94							0	
69	0	14-Apr-94							0	
64	0	18-May-94					1		1	
181	0	1-Jun-94							0	
63	0	13-Jun-94							0	
60	0	1-Jul-94							0	
62	0	2-Jul-94		1					1	
55	0	7-Jul-94							0	
56	0	13-Jul-94							0	
57	0	13-Jul-94							0	
58	0	13-Jul-94							0	
159	0	17-Jul-94			1				1	
172	0	24-Jul-94							0	
54	0	29-Jul-94							0	
53	0	7-Aug-94							0	
3	0	18-Aug-94							0	
51	0	24-Aug-94							0	
52	0	24-Aug-94							0	
50	0	5-Sep-94							0	
47	0	14-Sep-94							0	
48	0	15-Sep-94				1			1	
186	0	19-Sep-94		1					1	
43	0	27-Sep-94							0	
44	0	28-Sep-94				1			1	
45	0	4-Oct-94							0	
46	0	7-Oct-94			1	1			2	
42	0	18-Oct-94							0	
40	0	30-Oct-94							0	
41	0	30-Oct-94							0	
182	0	1-Nov-94							0	
187	0	7-Nov-94							0	
184	0	11-Nov-94					1		1	
167	0	14-Nov-94							0	
155	0	15-Nov-94				1			1	
165	0	17-Nov-94					1		1	
171	0	19-Nov-94							0	
177	0	21-Nov-94							0	
176	0	22-Nov-94		1					1	
160	0	29-Nov-94					1		1	
169	0	30-Nov-94							0	
178	0	30-Nov-94							0	
166	0	8-Dec-94							0	
168	0	8-Dec-94							0	
163	0	11-Dec-94							0	
175	0	11-Dec-94				1			1	
156	0	14-Dec-94		1					1	
179	0	15-Dec-94							0	
180	0	22-Dec-94							0	
161	0	27-Dec-94							0	
37	0	29-Dec-94					1		1	
162	0	29-Dec-94							0	
157	0	3-Jan-95		1					1	
188	0	3-Jan-95				1			1	
183	0	4-Jan-95							0	

File No.	Dose	Died	Brain	Pituitary	Bone	Epithelial	Thyroid	Mesenchymal	All H & N	Metaplasia
164	0	5-Jan-95							0	
185	0	5-Jan-95							0	
1	0	6-Jan-95							0	
38	0	6-Jan-95		1					1	
73	2	16-Dec-93		1					1	
102	2	27-Jan-94							0	
131	2	14-Mar-94							0	
6	2	29-Mar-94	1					1	2	
114	2	8-May-94							0	
144	2	13-May-94	1						1	
27	2	25-May-94		1					1	
11	2	3-Jun-94							0	
129	2	6-Jul-94							0	
4	2	1-Aug-94	1	1					2	
128	2	6-Aug-94							0	
127	2	19-Aug-94							0	
112	2	2-Sep-94		1					1	
201	2	5-Sep-94		1			1		2	
24	2	27-Sep-94		1					1	
94	2	12-Oct-94							0	
95	2	13-Oct-94	1	1					2	
82	2	19-Oct-94				1			1	
81	2	24-Oct-94	1						1	
140	2	24-Oct-94						1	1	
80	2	31-Oct-94							0	
189	2	31-Oct-94		1					1	
223	2	31-Oct-94							0	
196	2	6-Nov-94							0	
205	2	11-Nov-94					1		1	
226	2	11-Nov-94							0	
195	2	16-Nov-94							0	
215	2	18-Nov-94							0	
193	2	6-Dec-94		1					1	
216	2	7-Dec-94				1			1	
202	2	12-Dec-94		1			1		2	
214	2	15-Dec-94		1		2			3	
219	2	22-Dec-94		1			1		2	
194	2	29-Dec-94		1		1			2	
224	2	29-Dec-94							0	
200	2	3-Jan-95							0	
203	2	5-Jan-95							0	
212	2	5-Jan-95							0	
10	2	6-Jan-95		1					1	
92	2	6-Jan-95		1					1	
86	4	30-Jun-93							0	
104	4	25-Aug-93						1	1	
119	4	18-Oct-93							0	
148	4	13-Dec-93	1	1					2	
117	4	29-Dec-93							0	
133	4	24-Jan-94							0	
30	4	28-Jan-94		1					1	
132	4	4-Feb-94				1	1		2	
17	4	28-Feb-94							0	
16	4	7-Mar-94			1				1	
29	4	14-Mar-94						1	1	
28	4	22-Mar-94			1				1	
68	4	5-Apr-94				1			1	
100	4	19-Apr-94		1					1	
83	4	20-Apr-94				1			1	
115	4	20-Apr-94		1			1		2	
192	4	8-May-94		1			1		2	
12	4	10-May-94	1				1		2	

File No.	Dose	Died	Brain	Pituitary	Bone	Epithelial	Thyroid	Mesenchymal	All H & N	Metaplasia
5	4	13-Jun-94							0	
143	4	17-Jun-94		1					1	
59	4	26-Jun-94							0	
61	4	2-Jul-94							0	
26	4	6-Jul-94							0	
142	4	27-Jul-94		1					1	
126	4	5-Sep-94							0	
190	4	6-Sep-94		1					1	
96	4	7-Sep-94					1		1	
110	4	9-Sep-94		1		2			3	
49	4	27-Sep-94			1				1	
141	4	21-Oct-94		1					1	
93	4	30-Oct-94							0	
39	4	31-Oct-94		1			2		3	
197	4	1-Nov-94							0	
222	4	11-Nov-94				1	1		2	
208	4	16-Nov-94		1					1	
221	4	18-Nov-94							0	
227	4	21-Nov-94					1		1	
207	4	6-Dec-94					2		2	
213	4	22-Dec-94		1					1	
211	4	29-Dec-94					1		1	
150	8.5	19-Oct-93				2			2	
32	8.5	14-Jul-93						1	1	
85	8.5	20-Jul-93							0	
107	8.5	25-Aug-93							0	
120	8.5	18-Oct-93							0	
79	8.5	21-Oct-93							0	
125	8.5	15-Nov-93	1	1			1		3	
118	8.5	13-Dec-93					1		1	
135	8.5	15-Dec-93							0	
31	8.5	11-Jan-94							0	
147	8.5	31-Jan-94				1		1	2	
101	8.5	2-Feb-94		1					1	
116	8.5	9-Feb-94							0	
71	8.5	22-Feb-94							0	
18	8.5	23-Feb-94						1	1	
84	8.5	24-Feb-94				1	1		2	
70	8.5	2-Mar-94							0	
14	8.5	4-Apr-94		1		1	2		4	
15	8.5	5-Apr-94	1				2	1	4	
67	8.5	18-Apr-94					1		1	
146	8.5	18-Apr-94						1	1	
99	8.5	22-Apr-94				2	1		3	
13	8.5	3-May-94				1			1	
145	8.5	3-May-94				1			1	
65	8.5	19-May-94		1			1		2	
66	8.5	19-May-94							0	
98	8.5	19-May-94		1			1		2	
130	8.5	24-Jun-94						1	1	
191	8.5	20-Jul-94		1		1	1		3	
225	8.5	26-Jul-94						1	1	
111	8.5	7-Sep-94							0	
25	8.5	9-Sep-94			1				1	
2	8.5	12-Sep-94		1					1	
198	8.5	4-Nov-94		1					1	
206	8.5	16-Nov-94					2		2	
220	8.5	22-Dec-94					1	1	2	
209	8.5	27-Dec-94			1	2	1		4	
20	18	18-Oct-92							0	
21	18	18-Oct-92							0	
22	18	18-Oct-92							0	

File No.	Dose	Died	Brain	Pituitary	Bone	Epithelial	Thyroid	Mesenchymal	All H & N	Metaplasia
33	18	19-Oct-92							0	
34	18	19-Oct-92							0	
75	18	20-Oct-92							0	
76	18	20-Oct-92							0	
87	18	22-Oct-92							0	
88	18	22-Oct-92							0	
105	18	22-Oct-92							0	
106	18	29-Oct-92							0	
121	18	2-Nov-92							0	
137	18	3-Nov-92							0	
149	18	8-Nov-92							0	
151	18	10-Nov-92							0	
152	18	13-Nov-92							0	
199	18	9-Dec-92							0	
218	18	14-Dec-92							0	
23	18	31-Dec-92							0	
36	18	12-Jan-93							0	
91	18	13-Jan-93							0	
78	18	23-Jan-93							0	
124	18	22-Mar-93							0	
35	18	14-Apr-93							0	
139	18	17-May-93							0	
89	18	27-May-93							0	
90	18	3-Jun-93							0	
123	18	28-Jun-93							0	
138	18	12-Aug-93							0	
77	18	3-Oct-93							0	
7	18	28-Nov-93							0	
122	18	5-Jan-94							0	
154	18	15-Jan-94							0	
109	18	8-Feb-94							0	
19	18	9-Feb-94							0	
108	18	9-May-94							0	
113	18	10-May-94					1		1	